Influence of Age on Associations Between Childhood Risk Factors and Carotid Intima-Media Thickness in Adulthood

The Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium

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Background—Atherosclerosis has its roots in childhood. Therefore, defining the age when childhood risk exposure begins to relate to adult atherosclerosis may have implications for pediatric cardiovascular disease prevention and provide insights about the early determinants of atherosclerosis development. The aim of this study was to investigate the influence of age on the associations between childhood risk factors and carotid artery intima-media thickness, a marker of subclinical atherosclerosis.

Methods and Results—We used data for 4380 members of 4 prospective cohorts—Cardiovascular Risk in Young Finns Study (Finland), Childhood Determinants of Adult Health Study (Australia), Bogalusa Heart Study (United States), and Muscatine Study (United States)—that have collected cardiovascular risk factor data from childhood (age 3 to 18 years) and performed intima-media thickness measurements in adulthood (age 20 to 45 years). The number of childhood risk factors (high [highest quintile] total cholesterol, triglycerides, blood pressure, and body mass index) was predictive of elevated intima-media thickness (highest decile) on the basis of risk factors measured at age 9 years (odds ratio [95% confidence interval] 1.37 [1.16 to 1.61], P=0.0003), 12 years (1.48 [1.28 to 1.72], P<0.0001), 15 years (1.56 [1.36 to 1.78], P<0.0001), and 18 years (1.57 [1.31 to 1.87], P<0.0001). The associations with risk factors measured at age 3 years (1.17 [0.80 to 1.71], P=0.42) and 6 years (1.20 [0.96 to 1.51], P=0.13) were weaker and nonsignificant.

Conclusions—Our analyses from 4 longitudinal cohorts showed that the strength of the associations between childhood risk factors and carotid intima-media thickness is dependent on childhood age. On the basis of these data, risk factor measurements obtained at or after 9 years of age are predictive of subclinical atherosclerosis in adulthood. (Circulation. 2010;122:2514-2520.)

Key Words: pediatrics ■ risk factors ■ carotid atherosclerosis ■ epidemiology

Atherosclerotic diseases such as coronary heart disease, stroke, and peripheral artery disease are threats to global public health. Although these complications of atherosclerosis occur in the middle-aged or elderly, the pathophysiological process begins in childhood.1–3 Therefore, it would be beneficial to identify those children and adolescents with the highest risk as early in life as possible, so that interventions to reduce cardiovascular risk could be targeted. Indeed, there are existing guidelines on screening of dyslipidemia, elevated blood pressure, and obesity in childhood4–6; however, there is a shortage of data on the optimal age for screening of cardiovascular disease (CVD) risk factors in childhood.7

Editorial see p 2493
Clinical Perspective on p 2520
Four large studies of CVD risk factors initiated in childhood have followed study subjects into adulthood: The Cardiovascular Risk in Young Finns Study (Young Finns; Finland), the Childhood Determinants of Adult Health (CDAH) Study (Australia), the Bogalusa Heart Study (Bogalusa; United States), and the Muscatine Study (Muscatine; United States). In previous reports from these cohorts, it has been shown that CVD risk factors such as dyslipidemia, elevated blood pressure, and obesity identified in youth predict subclinical markers of atherosclerosis in the form of lesions in the aorta and coronary arteries measured at autopsy, as well as increased carotid artery intima-media thickness (IMT) measured by noninvasive ultrasound.8–12

In the present study, our main aim was to examine the influence of childhood age on the associations between childhood risk factors and carotid IMT in adulthood. This information may have implications for pediatric cardiovascular prevention and provide insights about the early determinants of atherosclerosis development. The analyses were based on 4380 subjects 3 to 18 years of age at baseline from the 4 cohort studies for whom data on childhood cardiovascular risk factors and carotid IMT in adulthood (mean follow-up 22.4 years) were available.

Methods
Data from 4 prospective cohort studies conducted in Finland (Young Finns), Australia (CDAH), and the United States (Bogalusa, Muscatine) were used. Each study received ethical approval, and written informed consent was obtained from the study subjects or their parents. All laboratory measurements were performed with fasting samples. For the statistical analyses, we included those subjects with complete risk factor data for each study year.

Cardiovascular Risk in Young Finns Study
Study Sample
The Young Finns sample is described in detail elsewhere.13 In the present study, we included 2653 subjects (74% of those eligible) who were 3, 6, 9, 12, 15, or 18 years old in 1980, 1983, or 1986 and who had carotid artery ultrasonography data from 2001 or 2007 (age 20 to 45 years). To maximize the available measurements within each age group, subjects with childhood data from up to 3 different time points were entered into as many as 3 different analyses, eg, a 6-year-old measured in 1980 who was subsequently followed up in 1983 (9 years old) and in 1986 (12 years old).

Clinic Measurements
Serum cholesterol and triglyceride concentrations were determined by enzymatic methods. High-density lipoprotein cholesterol (HDL-C) was analyzed after precipitation of very-low-density lipoprotein and low-density lipoprotein cholesterol (LDL-C) with dextran sulfate 500 000. LDL-C was calculated with the Friedewald equation. At baseline and follow-up, height and weight were measured, and body mass index (BMI) was calculated. Blood pressure measurements were obtained with a standard mercury sphygmomanometer at baseline. The mean of 2 measurements was used in the analyses.

Carotid Artery Ultrasound Studies
B-mode ultrasound studies of the carotid artery were performed with a validated portable Acuson Cypress (Siemens Medical Solutions USA Inc, Mountainview, Calif) ultrasound machine with a 7.0-MHz linear-array transducer by a single technician who traveled to field clinics.16 The ultrasound technician followed carotid artery imaging protocols described by the Young Finns study.10 Several 3- to 5-second real-time images were recorded that included the beginning of the carotid bulb and approximately 30 mm of the common carotid artery. From these images, the 2 highest-quality end-diastolic frames were selected by the reader for measurement. From each of these images, 6 measurements of the common carotid far wall were taken approximately 10 mm before the border of the carotid bulb to derive mean and maximum carotid IMT. Intrarater reproducibility for replicate maximum IMT measurements was assessed in a random sample of 30 subjects. The average absolute difference and SD was 0.02±0.04 mm.

The Bogalusa Heart Study
Study Sample
The Bogalusa Heart study sample has been described in detail elsewhere.8 For the present study, 593 subjects (12% of those eligible) 5 to 18 years old during childhood surveys (1981–1982, 1984–1985, or 1987–1988) who had carotid artery ultrasound at follow-up (either 2001–2002 or 2003–2007, age 20 to 43 years) were included. Subjects with childhood data from as many as 3 different time points were included in up to 3 different age-group analyses.

Clinic Measurements
Serum cholesterol and triglyceride levels were measured with a Technicon Auto Analyzer II (Technicon Instrument Corp, Tarrytown, NY) according to the laboratory manual of the Lipid Research Clinics program.15 Serum lipoprotein cholesterol levels were analyzed by a combination of heparin-calcium precipitation and agar–agarose gel electrophoresis procedures. Height and weight were measured at all time points, and BMI was calculated. Blood pressures were recorded with a mercury sphygmomanometer. Three blood pressure readings were taken by each of 2 randomly assigned observers for a total of 6 measurements. The mean of the 6 replicate readings was used in the analyses.

Carotid Artery Ultrasound Studies
B-mode ultrasound examinations were performed according to protocols described previously.11 Maximum IMT measurements were taken from both left and right common carotid, carotid bifurcation, and internal carotid segments. Seventy-five subjects underwent repeat ultrasound examinations 10 to 12 days after their initial visit to determine intraindividual reproducibility. The average absolute difference and SD between measurements for all carotid IMT segments was 0.015±0.013 mm.

The CDAH Study
Study Sample
The CDAH sample has been described in detail elsewhere.14 In the present study, we included data from 415 subjects (25% of those eligible) who were 9, 12, or 15 years old at baseline and who had risk factor data from baseline (1985) and carotid artery ultrasound measurements at follow-up at ages 28 to 36 years (2004–2006).

Clinic Measurements
In 1985, serum total cholesterol and triglycerides were determined according to the Lipid Research Clinics Program,15 and HDL-C was analyzed after precipitation of apolipoprotein-B–containing lipoproteins with heparin-manganese. LDL-C concentration was calculated with the Friedewald formula. Height and weight were measured, and BMI was calculated. Blood pressure measurements were obtained with a validated portable Acuson Cypress (Siemens Medical Solutions USA Inc, Mountainview, Calif) ultrasound machine with a 7.0-MHz linear-array transducer by a single technician who traveled to field clinics.16 The ultrasound technician followed carotid artery imaging protocols described by the Young Finns study.10 Several 3- to 5-second real-time images were recorded that included the beginning of the carotid bulb and approximately 30 mm of the common carotid artery. From these images, the 2 highest-quality end-diastolic frames were selected by the reader for measurement. From each of these images, 6 measurements of the common carotid far wall were taken approximately 10 mm before the border of the carotid bulb to derive mean and maximum carotid IMT. Intrarater reproducibility for replicate maximum IMT measurements was assessed in a random sample of 30 subjects. The average absolute difference and SD was 0.02±0.04 mm.

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The Muscatine Study

Study Sample
Between 1970 and 1981, 11 377 school children 8 to 18 years of age in Muscatine, Iowa, underwent 26 919 biennial examinations. Relevant to the analysis reported herein, between 1996 and 1999, 719 individuals (29% of those eligible) 33 to 42 years old who were representative of the childhood participants had carotid ultrasound examinations if they had previously participated in at least 1 childhood survey and 2 young adult surveys.

Clinic Measurements
Childhood measurements included total cholesterol and triglycerides, measured by use of an automated, colorimetric enzymatic assay. Height was recorded to the nearest 0.5 cm with the Iowa Stadiometer, and weight was recorded to the nearest 0.1 kg. Three random-zero blood pressures were recorded on each subject after a 5-minute seated rest by measurement of pulse obliteration pressure.

Carotid Artery Ultrasound Studies
Carotid ultrasound studies were performed by a single technician using the Biosound Phase 2 ultrasound machine and a 10-MHz probe (Biosound Esaote Inc, Indianapolis, Ind). The protocol for carotid ultrasound included measurement of the maximal IMT of the near and far wall of the common carotid, carotid bifurcation, and internal carotid arteries bilaterally. A 4.4% random sample underwent repeat carotid ultrasound studies during a second visit a mean of 107 days later to assess intrasubject reliability. The mean absolute difference for within-subject reliability was 0.058 mm with a median of 0.049 mm for the mean of the 12 maximal IMT measurements.

IMT Segment and Classification of High Carotid IMT in Adulthood
The maximum IMT measurement from the far wall of the left common carotid artery was used for analysis because it was the only consistent segment of the carotid tree examined across the 4 studies. We defined high IMT in adulthood as an IMT ≥90th percentile for age-, sex-, race- (Bogalusa), study year-, and cohort-specific values to account for any method, secular, or cohort differences.

Statistical Analyses
Because the Young Finns study had the largest sample size, we used age groups (3, 6, 9, 12, 15, and 18 years) from that cohort as a basis to form age groups from the remaining cohorts. Age groups for CDAH (9, 12, and 15 years) were consistent, but age groups for Bogalusa and Muscatine were constructed to include ages 5 to 7, 8 to 10, 11 to 13, 14 to 16, and 17 to 19 to approximate the 6-, 9-, 12-, 15-, and 18-year-old age groups in Young Finns.

To take into account possible differences due to age, sex, race, secular trends in risk factors, different study cohorts, and different methodology, we first performed these analyses separately in the 4 cohorts. Thereafter, the analyses were repeated using the number of risk factors in the highest quintile (ie, standardized for age, sex, race, study year, and study cohort). The ability of the childhood risk score (treated as a continuous variable) to predict highest-decile IMT in adulthood at different ages was assessed by logistic regression analysis. We first performed these analyses separately in the 4 cohorts. Thereafter, the analyses were repeated with data pooled from all cohorts. To examine the consistency of our results, we performed reanalyses defining risk factors by use of existing guidelines for borderline-high/high levels of total cholesterol and triglycerides, prehypertension/hypertension, and overweight/obesity. To study the associations between individual childhood risk factors and IMT in adulthood (treated as a continuous variable) in different age groups, we used linear regression analysis.

All statistical analyses were performed with STATA 10 (Stata-Corp LP, College Station, Tex). Statistical significance was inferred at a 2-tailed P<0.05.

Results

Participant Characteristics
Key baseline characteristics for subjects in each cohort are displayed in Table 1. The mean (SD) time between baseline and follow-up was 22.4 (3.7) years.

Influence of Age on Associations Between Childhood Risk Score and High IMT in Adulthood
Table 2 shows the ability of childhood risk score to predict high adult IMT on the basis of logistic regression models. In pooled analyses that included data from all 4 cohorts, significant associations were observed with risk factors measured at ages 6, 9, 12, 15, or 18 years in males and ages 9, 12, 15, and 18 years.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Study Subjects</th>
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<tbody>
<tr>
<td>No. of subjects (males/females)</td>
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<tr>
<td>----------------------------------</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Age range at baseline</td>
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<tr>
<td>Age range at follow-up</td>
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<tr>
<td>Follow-up time, y, mean (range)</td>
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<tr>
<td>Blacks, %</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
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<td>LDL-C, mmol/L</td>
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<tr>
<td>HDL-C, mmol/L</td>
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<tr>
<td>Triglycerides, mmol/L</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>Systolic BP, mmHg</td>
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<tr>
<td>Diastolic BP, mmHg</td>
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</table>

Young Finns indicates Cardiovascular Risk in Young Finns Study; CDAH, Childhood Determinants of Adult Health Study; Bogalusa, Bogalusa Heart Study; Muscatine, Muscatine Study; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; and BP, blood pressure.

Values are mean (SD) unless otherwise stated.
in females. When we explored the heterogeneity between different studies, the greatest discrepancies in the odds ratios between risk score and high IMT were seen in those strata with smaller numbers of observations (<100).

In the analyses performed without the Young Finns data, the childhood risk score r... in those strata with smaller numbers of observations (<100).

As shown in the Figure, the results were essentially similar to those observed in Table 2 when existing guidelines for abnormal childhood risk factor levels were used in place of standardized (age, sex, race, study year, and study cohort) cut points. In addition, the findings were similar when the analyses were performed without triglyceride values or when systolic blood pressure was replaced with diastolic blood pressure (data not shown). In general, in all analyses, the largest odds ratios were observed among 15- and 18-year-olds.

In addition to data provided in Table 2 and the Figure, we performed analyses using LDL-C and HDL-C instead of total cholesterol with data from the Young Finns, CDAH, and Bogalusa studies (these risk factors were not measured at baseline in the Muscatine Study). In the pooled analyses for the 3 cohorts, the results were essentially similar to those with total cholesterol (data not shown).

### Analyses of Individual Childhood Risk Factors and Adult Carotid IMT

Tables 3 shows age-specific results of multivariable analyses studying the independent associations of different childhood risk factors with IMT in adulthood (treated as a continuous variable) in pooled data. In these analyses, total cholesterol levels were associated with IMT among 12-, 15-, and 18-year-old subjects. Systolic blood pressure was associated with IMT among 6-, 12-, 15-, and 18-year-olds. BMI had a significant association in all other age groups but not in 6-year-olds. In analyses in which diastolic blood pressure levels were used instead of systolic blood pressure, they were not associated with IMT in any of the age groups.

The multivariable models were repeated with a dichotomous IMT outcome (highest decile). In these analyses, the main differences compared with results in Table 3 were observed among 18-year-olds, as the effects of total cholesterol (odds ratio [95% confidence interval] for a 1-SD change 1.17 [0.99 to 1.40]) and systolic blood pressure (1.17 [0.94 to 1.36]) were nonsignificant. In addition, among 3-year-olds, BMI was not significantly associated with high IMT (odds ratio 1.08, 95% confidence interval 0.76 to 1.53). Otherwise, the significant associations observed with continuous IMT data were not altered.

In addition to data provided in Table 3, we performed analyses using LDL-C, non–HDL-C, and HDL-C data instead of total cholesterol from the Young Finns, CDAH, and Bogalusa studies. In these pooled analyses for 3 cohorts, LDL-C and non–HDL-C were significantly associated with IMT among 12-, 15-, and 18-year-olds. We found no significant inverse relation between HDL-C and IMT in any age group.

### Discussion

Our results using data from the 4 large prospective cohorts that have followed up individuals from childhood to adulthood suggest that the age of risk factor assessment is an important consideration in the identification of children who will be at increased risk of having subclinical atherosclerosis in young adulthood (age 20 to 45 years). On the basis of our
findings, risk factors measured before the age of 9 years have only weak or nonsignificant associations with carotid IMT measured more than 20 years later, whereas analysis among subjects 9 to 18 years of age showed significant associations between childhood risk exposure and increased adult IMT.

Previously, data from the Young Finns cohort\textsuperscript{10,20} have shown that when subjects 3 to 9 years old or 12 to 18 years old are compared at baseline, the associations between conventional risk factors and apolipoproteins with IMT are stronger in the older age groups. In the present study, we examined all the age groups in the Young Finns Study (3-, 6-, 9-, 12-, 15-, and 18-year-olds) separately. In addition, we performed analyses on the effect of age in 3 other cohorts (CDAH, the Bogalusa Heart Study, and the Muscatine Study) that have collected childhood risk factor data and adult carotid IMT measurements. When risk factor data on lipids, blood pressure, and BMI were combined into a simple risk score, consistent associations both among males and females were found between childhood risk profile and high IMT in adulthood among subjects 9, 12, 15, and 18 years of age. However, among 3-year-olds, there were no significant associations, and among 6-year-olds, only a weak significant association was observed among males, whereas in female-specific or sex-combined analyses, no significant results were seen. It may be argued that the statistically weaker associations in younger age groups are due to smaller sample sizes in these cohorts. However, the odds ratio values were clearly higher with increasing age, which suggests a true age trend. With regard to individual risk factors, the results for age trends were similar. The improvements in these associations by age were weaker and not as consistent as for the risk score.

Several guidelines on childhood CVD risk factor screening based on individual risk factors exist. The National High Blood Pressure Education Program issued guidelines for the diagnosis, evaluation, and treatment of high blood pressure that suggested that all children $\geq$ 3 years old who are seen in a medical setting should have their blood pressure measured.\textsuperscript{5} In a recent statement by a US Preventive Services Task Force, a grade B recommendation was given that clinicians should screen children 6 years of age and older for obesity.\textsuperscript{6} The American Academy of Pediatrics recommended selective lipid screening for children as young as 2 years of age who have a positive family history of hypercholesterolemia or premature ($\leq$ 55 years of age for men and $\leq$ 65 years of age for women) CVD. It is also recommended that pediatric patients for whom family history is not known or those with other CVD risk factors, such as overweight (85th percentile $\leq$ BMI $<$ 95th percentile), obesity (BMI $<$ 95th percentile), hypertension (blood pressure $>$ 95th percentile), cigarette smoking, or diabetes mellitus, be screened with a fasting lipid profile.\textsuperscript{4} In the present study, we examined the effect of risk factor measurement age on predicting the incidence of subclinical atherosclerosis. In the setting of CVDs, the present results suggest that to recognize the high-risk subjects for early atherosclerosis, risk factor measurements are the most useful after the age of 9 years. However, because the ability to impact lifestyle might be greater at younger ages, the identification of risk in the teenage years might be too late to make substantive changes. Indeed, the results from the Special Turku Coronary Risk Factor Intervention Project for children (STRIP) have shown that a low-saturated-fat diet intervention initiated in infancy is both safe and efficient in terms of reducing cholesterol levels and improving brachial endothelial function.\textsuperscript{21-23} In line with this, in the Dietary Intervention Study in Children (DISC), dietary behavioral intervention started at the age of 8 to 10 years among children with elevated LDL-C levels was associated with improved cholesterol levels.\textsuperscript{24}

Age-related differences in the tracking of cardiovascular risk factors are the most plausible explanation for our findings concerning the age difference in the associations between childhood risk factors and IMT in adulthood. It has been shown that the strength of tracking of lipids, blood pressure, and BMI from childhood to adulthood is stronger with increased baseline age.\textsuperscript{25-27} It is possible that the cross-sectional risk factor measurements also reflect a cumulative lifetime risk factor burden, and therefore, the associations with subclinical atherosclerosis are stronger with increasing age. However, we only had data available on 3-year-olds from the Young Finns cohort and on 6-year-olds from the Young Finns and Bogalusa cohorts. Therefore, the nonsignificant findings in these age groups should be interpreted cautiously. Nevertheless, these
Our analyses from 4 longitudinal cohort studies showed that the strength of the associations between childhood risk factors and adult carotid IMT are dependent on childhood age. On the basis of these data, risk factor measurements performed at or after 9 years of age are predictive of subclinical atherosclerosis in adulthood.

Acknowledgments
We gratefully acknowledge the contributions of data collection teams at all measurement time points across all study centers. Above all, we thank the individuals who participated as both children and adults in these longitudinal studies.

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Disclosures
None.

References

Table 3. Sex- and Cohort-Pooled Analyses of Multivariable Associations Between Childhood Risk Factors and Adult Carotid IMT for Each Age Group

<table>
<thead>
<tr>
<th>Age Groups, y</th>
<th>3*</th>
<th>6†</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
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<td>n</td>
<td></td>
<td></td>
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<tr>
<td>Total cholesterol</td>
<td>0.056±0.047</td>
<td>0.051±0.033</td>
<td>0.012±0.024</td>
<td>0.082±0.022</td>
<td>0.058±0.021§</td>
<td>0.071±0.027§</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.024±0.047</td>
<td>-0.033±0.033</td>
<td>0.033±0.025</td>
<td>-0.026±0.024</td>
<td>0.024±0.022</td>
<td>0.002±0.027</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.002±0.048</td>
<td>0.102±0.033§</td>
<td>0.041±0.025</td>
<td>0.078±0.023§</td>
<td>0.063±0.022§</td>
<td>0.064±0.027‡</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.101±0.047‡</td>
<td>0.059±0.032</td>
<td>0.081±0.026§</td>
<td>0.124±0.024§</td>
<td>0.112±0.023</td>
<td></td>
</tr>
</tbody>
</table>

Data are β±SE.
*Model includes data from Young Finns Study only.
†Model includes data from Young Finns and Bogalusa studies only.
§P<0.05, †P<0.01, ‡P<0.001.

*Data suggest that based on risk factor assessments, high-risk individuals could be identified from the age of 9 years onward.**

Study Limitations
The strength of the present study is the ability to combine data on childhood risk factors and adult carotid IMT from 4 large longitudinal cohorts around the world. However, the study has a number of potential limitations. First, heterogeneity in the IMT location and ultrasound protocols existed among the cohorts. Even though we attempted to take this heterogeneity into account by defining IMT according to age-, sex-, race- (Bogalusa only), study year–, and cohort-specific values, we note that attempts by future investigators to merge imaging studies will also face this limitation until calls for method standardization are observed. Second, carotid IMT measurements were performed in the common carotid artery. A more complex carotid IMT score involving both the internal and common carotid may have better predictive value than either measure taken alone. However, the association between carotid and coronary atherosclerosis is only marginally increased when information about IMT from the internal carotid and carotid bulb is added to that of the common carotid IMT, which supports the use of common carotid IMT. Third, because the study cohorts comprised young adults, we were not able to study associations between risk factors and cardiovascular events. Instead, we used vascular ultrasound measures as indicators of an atherogenic process. We examined the effect of multiple risk factors using a simple sum score. Although we found a relationship between the risk score and high IMT, a clinically more useful way would be a risk calculator such as the Framingham score developed in adults. Therefore, future studies to construct a childhood risk model are needed, especially when data are available on clinical end points from the cohorts that have childhood risk factor measurements. Fourth, the childhood data from the Muscatine Study were gathered 10 to 15 years earlier than those from other cohorts. Although we used cohort- and study year–specific risk factor values in the analyses, birth cohort effects from the Muscatine Study were gathered 10 to 15 years earlier than those from other cohorts. Although we used cohort- and study year–specific risk factor values in the analyses, birth cohort effects and cohort-specific values, we note that attempts by future investigators to merge imaging studies will also face this limitation until calls for method standardization are observed. Second, carotid IMT measurements were performed in the common carotid artery. A more complex carotid IMT score involving both the internal and common carotid may have better predictive value than either measure taken alone. However, the association between carotid and coronary atherosclerosis is only marginally increased when information about IMT from the internal carotid and carotid bulb is added to that of the common carotid IMT, which supports the use of common carotid IMT. Third, because the study cohorts comprised young adults, we were not able to study associations between risk factors and cardiovascular events. Instead, we used vascular ultrasound measures as indicators of an atherogenic process. We examined the effect of multiple risk factors using a simple sum score. Although we found a relationship between the risk score and high IMT, a clinically more useful way would be a risk calculator such as the Framingham score. Therefore, future studies to construct a childhood risk model are needed, especially when data are available on clinical end points from the cohorts that have childhood risk factor measurements. Fourth, the childhood data from the Muscatine Study were gathered 10 to 15 years earlier than those from other cohorts. Although we used cohort- and study year–specific risk factor values in the analyses, birth cohort effects and cohort-specific values, we note that attempts by future investigators to merge imaging studies will also face this limitation until calls for method standardization are observed.


CLINICAL PERSPECTIVE

The pediatric origin of atherosclerosis is now well accepted, with several authorities issuing guidelines and consensus statements for the assessment and management of cardiovascular disease risk factors, including lipids and lipoprotein, blood pressure, and adiposity, in childhood. Despite this, there have been scant data that have assessed the optimal age when childhood risk exposure begins to associate with adult atherosclerosis, and thus the optimal age for risk factor screening. In the present analyses based on 4 population-based, prospective childhood cohorts—the Cardiovascular Risk in Young Finns Study (Finland), the Childhood Determinants of Adult Health study (Australia), the Bogalusa Heart Study (United States), and the Muscatine Study (United States)—we examined the influence of age on the associations between childhood risk factors and adult carotid artery intima-media thickness, a subclinical marker of atherosclerosis, among 4380 participants 3 to 18 years old at baseline who were reexamined 13 to 28 years later. On the basis of our findings, risk factors measured before the age of 9 years had only weak or nonsignificant associations with carotid intima-media thickness measured more than 20 years later, whereas analysis among subjects 9 to 18 years of age showed significant associations between childhood risk exposure and increased adult intima-media thickness. Our data have direct clinical and public health importance because they suggest that risk factor screening from the age of 9 years onward allows youth who are at increased risk of subclinical atherosclerosis in adulthood to be identified. However, care providers need to keep in mind that although the optimal age for pediatric risk factor screening may commence at 9 years of age, primordial prevention of cardiovascular disease should begin earlier in the life course.
Influence of Age on Associations Between Childhood Risk Factors and Carotid Intima-Media Thickness in Adulthood: The Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium

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소아 및 청소년에서 연체 심혈관계 위험인자를 검사해야 성인이 된 후 정동맥 내막-중막 비후를 예측할 수 있을까?

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Summary

배경
족상동맥 경화증의 발생은 소아 시기에 이미 부리라는 주제. 소아~청소년기의 어느 연령대에서 심혈관계 위험인자 노출될 때 성인이기 때문에 심혈관계 경화증이 더 잘 발생하는 지 알 수 있다. 심혈관계 질환을 예방하는 데 도움이 되며, 특히 연령부터 증상적인 관리가 필요할 것인지에 대한 계획도 세울 수 있다. 따라서 이 연구는 소아~청소년기 심혈관계 위험인자와 정상인의 총 혈액응고제의 위험인자를 비교하여 연령에 따른 영향을 미치는지를 알아보고자 하였다.

방법 및 결과
소아 및 청소년기(3-18세)의 심혈관계 위험인자와 성인기(20-45세)의 정동맥 내막-중막 두께를 추정된 4개의 전형적 코호트 연구의 4,380명을 대상으로 하였다. 이를 4개의 코호트 연구는 Cardiovascular Risk in Young Finns Study(Finland), Childhood Determinants of Adult Health Study(Australia), Bogalusa Heart Study(United States), Muscatine Study(United States) 이다. 소아기의 심혈관계 위험인자는 중 글라스테폴, 중심지방, 혈압, 총혈액응고종 각 코호트에서 80% 이상인 것으로 정의하였고, 정동맥 내막-중막 두께의 증가는 각 코호트에서 90% 이상인 것으로 정의하였다. 연령에 따른 예측의 적합성을 통계적으로 분석한 결과, 9세(CR, 1.37; 95% CI, 1.16-1.61; P<0.0003), 12세(CR, 1.48; 95% CI, 1.28-1.76; P<0.0001), 15세(CR, 1.56; 95% CI, 1.36-1.78; P<0.0001), 18세(CR, 1.57; 95% CI, 1.31-1.87; P<0.0001)에서 통계적으로 유의한 연관성이 있었다. 3세(CR, 1.17; 95% CI, 0.80-1.71; P=0.42)와 6세ОР(CR, 1.20; 95% CI, 0.86-1.51; P=0.13)에서는 통계적인 유의성이 없었다.

결론
4개의 전형적이고 정기적인 코호트 연구를 분석한 결과에서 알 수 있듯이 소아기 심혈관계 위험인자와 성인기에서의 정동맥 내막-중막 두께에 공극적으로 영향을 미치고 있다. 이에 따르면 소아의 심혈관계 위험인자로는 중 글라스테폴, 중심지방, 혈압, 총혈액응고종 각 코호트에서 80% 이상인 것으로 정의하였고, 정동맥 내막-중막 두께의 증가는 각 코호트에서 90% 이상인 것으로 정의하였다. 연령에 따른 예측의 적합성을 통계적으로 분석한 결과, 9세(CR, 1.37; 95% CI, 1.16-1.61; P<0.0003), 12세(CR, 1.48; 95% CI, 1.28-1.76; P<0.0001), 15세(CR, 1.56; 95% CI, 1.36-1.78; P<0.0001), 18세(CR, 1.57; 95% CI, 1.31-1.87; P<0.0001)에서 통계적으로 유의한 연관성이 있었다. 3세(CR, 1.17; 95% CI, 0.80-1.71; P=0.42)와 6세(ОР, 1.20; 95% CI, 0.86-1.51; P=0.13)에서는 통계적인 유의성이 없었다.
우리 민족의 비극적인 한국전쟁을 배경으로 한 중요한 연구가 발표되었다. Enos 등이 진행한 이 연구는 전산점 검은 군영(군영 전쟁 223) 300명의 환상동작 두통 소견에 관한 것으로, 20대의 검은 나이에도 불구하고 약 77.3%에서 이미 전산점 검은 환상동작 측정작업환경에 진단되었고, 전산점 검은 대다수이다. 그리고 보고하였다. 이는 환상동작 검은의 임상양상이 연속이 buffers이 제시되었고, 이의 체소형 사이트에서도 발생하고 진행되므로 위험인자를 감소시키는 시도를 조기 시각해야 한다는 시도를 일찍 하였다. 연구에 참여한 연구원들은 이러한 연구가 진행되었다. 이들이 빈도로 게재된 연구와의 차이점은, 이는 실시간 검은의 인터넷 조사로 행사를 진행하여, 전산점 검은의 임상양상이 연속이 buffers이다. 그리고 이에 대한 연구가 진행되었다. 이들 연구들도 우리가 새롭게 발견한 위험인자들의 검은 상호작용이 존재하는 것을 grade B recession으로 제시하였다.

그러나 아직까지 실험한 위험인자들은 아직도 임상적 연구가 필요하다고 하여. 본 연구에서도 연구 대상으로 진단된 4개의 연구에서는 자료를 얻어 분석하였다. 주요 결과는 소년기에 실험한 위험인자가 많은 경우에 상당히 높은 경도의 내각 중심 두통의 문제가 증가함으로써 위험인자가 많으면 적은 경우로도 경도의 내각 중심 두통의 문제를 더욱 증가하였다. 가장 의미 있는 결과는 실험한 위험인자들 9개의 이에 대한 연구에서 환자의 경도의 내각 중심 두통의 증가율을 예측할 수 있다는 것이다. 이 실험은 길이와 직선된 두께에서 환자의 상호작용을 감사시키고 말할 때 위험인자와의 스트레스를 예방시켜야 하며 이를 감사시키는 노력을 해야 할 것이다. 이를 위한 방법을 볼 수 있다. 물론, 경도의 내각 중심 두통이 증가하는 것 혹은 경도의 내각 중심 두통이 적절한 것으로 환상동작 측정작업 환경의 전산점 검은 대다수이다. 그리고 사진에 있어서 미래의 실험한 사건의 발생과 밀접한 관계가 있을음을 보고하였다. 따라서 성인기 경도의 내각 중심 두통이 같거나 유사한 것으로 예측하는 경우 대체적인 증상을 통해 위험인자를 감소시키는 것이 중년 이후의 실험한 사건의 예방에 도움을 줄 것으로 추정될 수 있다. 그러나 이를 종합하여 보면 다른 사건이 필요하다고 생각된다.

본 연구는 4개의 다른 코호트 연구를 분석한 것이다. 특히, 브리태나 토폴의 연구는 도달된 정보가 통계적 분석에 여름, 경도의 영향을 각별한 차이를 보였다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높 은 연구에 서에서도 중요한 단축과 한계가 달라진 통계적 분석이 여름, 경도의 영향을 각별한 차이를 보였다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높은 연구에 서에서도 중요한 단축과 한계가 달라진 통계적 분석이 여름, 경도의 영향을 각별한 차이를 보았다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높은 연구에 서에서도 중요한 단축과 한계가 달라진 통계적 분석이 여름, 경도의 영향을 각별한 차이를 보았다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높은 연구에 서에서도 중요한 단축과 한계가 달라진 통계적 분석이 여름, 경도의 영향을 각별한 차이를 보았다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높은 연구에 서에서도 중요한 단축과 한계가 달라진 통계적 분석이 여름, 경도의 영향을 각별한 차이를 보았다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높은 연구에 서에서도 중요한 단축과 한계가 달라진 통계적 분석이 여름, 경도의 영향을 각별한 차이를 보았다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높은 연구에 서에서도 중요한 단축과 한계가 달라진 통계적 분석이 여름, 경도의 영향을 각별한 차이를 보았다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높은 연구에 서에서도 중요한 단축과 한계가 달라진 통계적 분석이 여름, 경도의 영향을 각별한 차이를 보았다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높은 연구에 서에서도 중요한 단축과 한계가 달라진 통계적 분석이 여름, 경도의 영향을 각별한 차이를 보았다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높은 연구에 서에서도 중요한 단축과 한계가 달라진 통계적 분석이 여름, 경도의 영향을 각별한 차이를 보았다. 그로 인해 본 연구는 새로운 연구는 연속적으로 빈도가 높은 연구에 서에도...